Report of a NTP Workshop -

"Animal Models for the NTP Rodent Cancer Bioassay: Strains & Stocks - Should We Switch?"

Presented to the
Board of Scientific Counselors
Thursday August 18, 2005
Angela King-Herbert

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First Roadmap Workshop

- **Animal Models for the NTP Rodent Cancer Bioassay: Strains & Stocks - Should We Switch?**
- **Held June 16-17, 2005 at NIEHS**
- **Morning lectures**
- **Three breakout groups**
  - **Mouse Models**
  - **Rat Models**
  - **Multiple Strain Approach**
- **Presentation and background materials available at http://ntp.niehs.nih.gov/ see "Meetings & Workshops"**

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Invited Panel

Workshop Chair: James Popp, Stratoxon LLC
Mouse Models:
- **Norman Drinkwater**, University of Wisconsin **(Chair)**
- **Molly Bogue,** Jackson Laboratory
- **John DiGiovanni,** University of Texas
- **Jeff Everitt**, GlaxoSmithKline
- **David Threadgill**, University of North Carolina

Rat Models:
- **Jerry Hardisty,** Experimental Pathology Labs **(Chair)**
- **Tom Hamm**, North Carolina State University (retired)
- **William Hooks**, Huntingdon Life Sciences
- **Dan Morton**, Pfizer
- **James Popp**, Stratoxon LLC
- **Carlos Sonnenschein**, Tufts University
- **Vernon Walker**, Lovelace Respiratory Research Institute

Multiple Strain Approach:
- **Julian Preston**, US Environmental Protection Agency **(Chair)**
- **Michael Festing**, University of Leicester (United Kingdom)
- **Joe Haseman**, National Institute of Environmental Health Sciences (retired)
- **Howard Jacob**, Medical College of Wisconsin
- **Ralph Kodell**, National Center for Toxicological Research
- **Hiroyoshi Toyshiba**, National Institute for Environmental Studies (Japan)

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Break out Group Charges

- **Rat Models**
- **Mouse Models**
- **Multiple Strain Approach**

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Rat Models

- Liabilities in the current strain of F344/N that NTP is using mandate that it should not be used.
  - Mutations (?) in the current strain appear to be causing (some of) these liabilities
- Three options:
  - Re-establish the F344/N strain (some liabilities still exist)
  - Create an F1 Hybrid (little or no historical database)
  - Choose an appropriate alternative strain/stock (such as outbred Wistar Han)
    - Outbred variability
    - Insensitive strain?

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Rat Models (cont)

- A multi-strain study would have to be scaled up appropriately to mimic a single strain study design, and therefore is not practical for a screening bioassay.

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Mouse Models

- Continued use of the mouse in bioassays is essential
- Isogenic strains should be used
  - F1 hybrids preferable to inbreds
- Liabilities associated with the current B6C3F1 are not yet critical enough to justify switching strains but could become so
  - Major liability is increasing incidence of liver tumors in control males (60%+), likely associated with increasing body weight
  - Need to understand basis for lower liver tumor background for B6C3F1 mice in NCTR studies

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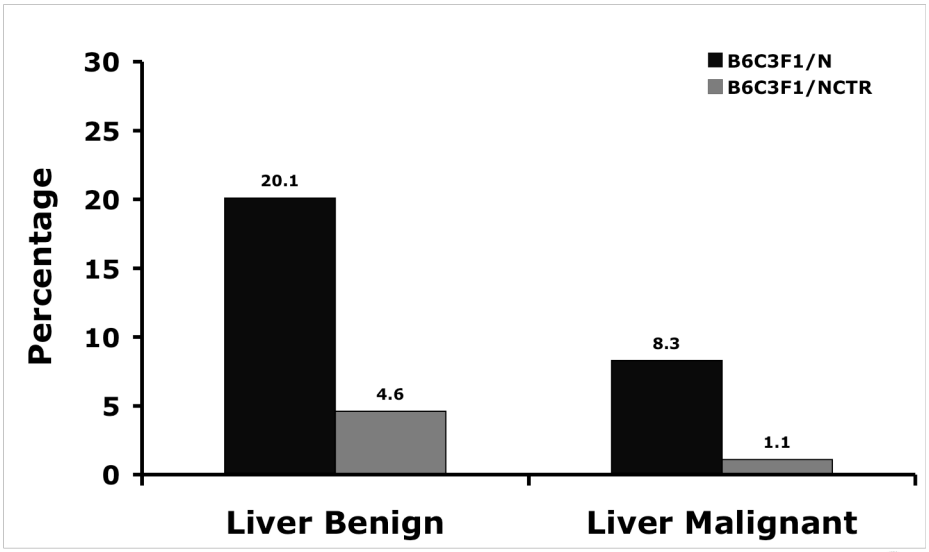
Female Mice Liver Tumors



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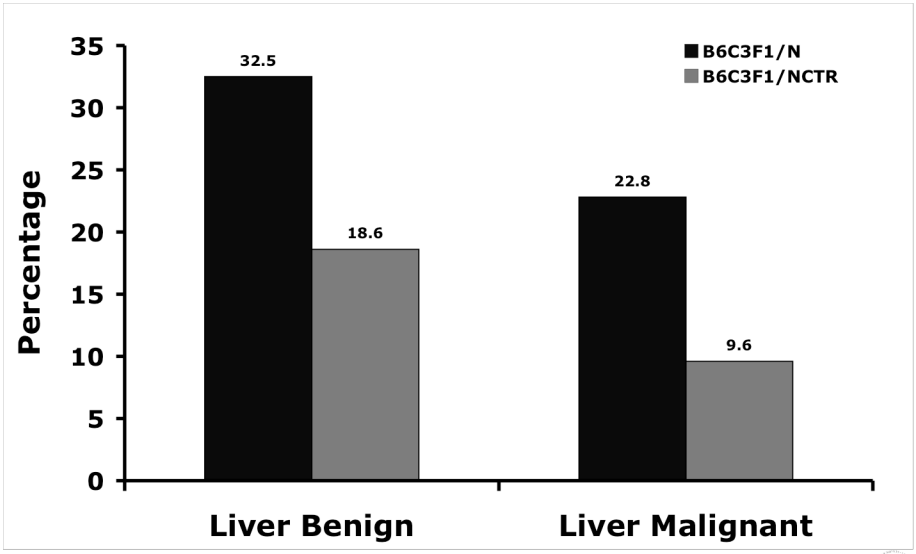
Male Mice Liver Tumors



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Mouse Models (cont)

If alternative model(s) is sought:

- **First implement as a 25x2 study, with equal numbers of B6C3F1 and the alternative hybrid**
- **Above approach would provide continuity with existing database while experience is gained with new model**

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Multiple Strain Approach

Advantages:

- **Better captures range of rodent genetic variability**
- **Statistical power advantage for heterogeneous responses without increasing the number of animals used in 2-year bioassay**
- **Help identify mechanisms of cancer induction and susceptibility**

Disadvantages:

- **Added cost (multiple 90-day MTD dose finding studies)**
- **More opportunity for operational error (e.g., more doses)**
- **Increased logistical problems with use of multiple strains**
- **Need to collect background data for strains**
- **If regulatory acceptance is an issue**

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Multiple Strain Approach (cont)

- **The NTP should consider use of multiple strains as a viable approach for cancer hazard identification**

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Multiple Strain Approach (cont)

- Isogenic (inbred and/or F1 hybrid)
- From a fixed pool of strains, select a subset of strains (e.g., 4) to test for a given agent
- Would want at least a minimal amount of 2-year historical control data for any strain selected
- Pooled analysis recommended
- Implement by incrementally adding strains to current 2-year bioassay

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Where Do We Go From Here?

- Mouse Model
  - No change to the current model
  - Consider multiple strain studies
- Rat Model
  - Identify new F344 line - Highest priority
  - Use a commercial source of the F344 line until the new line is ready
  - Explore F344/Brown Norway hybrid
- Outstanding issues (BSC Working Group)
  - Multiple Strain Approach
    - Consider cost benefit
    - Strain selection
      - Relation to mouse sequencing project
    - Design of studies
    - Analysis of data

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